

### **REMARKS**

The Examiner is thanked for the thorough examination of the application.

The present specification, Table 1, found at page 29 has been amended to address typographical issues. Namely, PO<sub>2</sub> (Torr) (tumor cells) in the 5<sup>th</sup> row of Table 1 has been amended to read PO<sub>2</sub> (Torr) (normal cells).

Claims 1, 3, 5 and 7-15 are pending in the application. Claim 6 has been canceled without prejudice or disclaimer of the subject matter contained therein. Claims 1 and 9 have been amended to clarify the meaning of variables R<sub>1</sub>, R<sub>4</sub>, and R<sub>11</sub>. Support for the present amendments may be found in canceled claim 6 and/or in the specification at page 11, lines 4-8, page 12, lines 5-12, page 13, lines 1-20 and page 14, lines 9-10. Applicants respectfully submit that no new matter has been added by way of the present amendments.

#### **Rejection Under 35 U.S.C. §112, First Paragraph**

Claims 1, 3, 5-15 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement with respect to the meanings of variables R<sub>1</sub> and R<sub>4</sub>. The present amendment to the claims clarifies the meaning of these variables and it is respectfully submitted that said amendment renders moot the outstanding rejection. Reconsideration and withdrawal of the rejection is earnestly solicited.

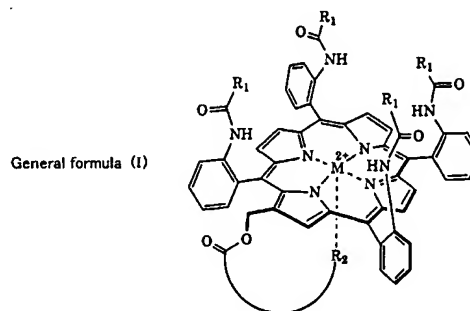
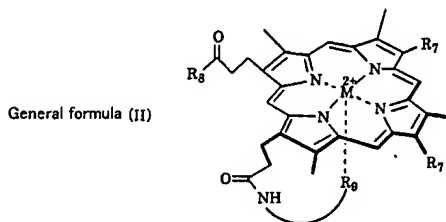
#### **Rejection Under 35 U.S.C. §103(a) Over Tsuchida I and Tsuchida II**

Claims 1-3 have been rejected under 35 U.S.C. §103(a) as being obvious over the combination of Tsuchida I (Tsuchida et al., Bioconjugate Chem., 1999, 10, 797-802) in view of Tsuchida II (Tsuchida et al., Bioconjugate Chem., 2000, 11, 46-50). Applicants respectfully traverse.

### *The Present Invention And Its Advantages*

The present invention provides an oxygen infusion for increasing the oxygen concentration in tumor tissues in living bodies and, more particularly, a highly-safe oxygen infusion for effectively increasing oxygen partial pressures in a hypoxic region of the tumor tissues by administering the infusion to a site near tumor tissues of human bodies. The present invention makes it possible to effectively increase the oxygen partial pressure in the tumor tissues by use of the porphyrin metal complex-clathrate albumin compound which has a molecular size smaller than that of red blood cells and which can easily pass through irregular blood vessels in the tumor tissues as compared with the red blood cells.

According to the present invention, the above object is achieved by providing an oxygen infusion formed from a dispersion liquid of one or more albumin clathrate compounds dispersed in a physiologically permissible aqueous media, the albumin clathrate compounds including a porphyrin metal complex represented by the general formula (I) or porphyrin metal complexes respectively expressed by the general formulas (I) and (II).



The porphyrin metal complex-clathrate albumin compound of the present invention makes it possible to effectively increase the oxygen partial pressure in the tumor tissues. In fact, the oxygen partial pressure is increased up to 2.5 time of the primary oxygen partial pressure ( $1.4 \pm 0.2$  Torr) by administration of the oxygen infusion product of the present invention, as demonstrated by Example 1 in the specification.

Example 1 discloses that the prepared porphyrin metal complex is 2-8-(2methyl-1-imidazolyl) octanoyloxymethyl-5, 10, 15, 20-tetrakis-( $\alpha$ ,  $\alpha$ ,  $\alpha$ ,  $\alpha$ -o-pivaloylarnidophenyl) porphyrin iron(II) complex, which is expressed by the formula (I) in which R1 is pivaloyl, R2 is a basic axial ligand expressed by the formula (A) in which R3 is alkylene and R4 is methyl. An albumin-Heme (carbon monoxide complex) solution prepared from the above porphyrin metal complex and human serum albumin, was exposed to oxygen and irradiated with light to prepare an oxygen-saturated albumin-Heme solution, which may be called an "oxygen-saturated sample." (page 25, last paragraph).

The oxygen-saturated samples were administered by intra-arterial injection to rats with cancer transplanted into right femurs. Simultaneously with the initiation of intra-arterial injection, measurements were made on the partial pressures of oxygen at both tumor sites and normal sites to determine sequential changes of the oxygen partial pressure. After completion of measurements, an incision is made at the abdominal area and then measurements are made on size of the tumor.

For the rHSA-Heme treated group, the primary partial pressures of oxygen (P02) at the normal sites and tumor sites of the right leg were  $15.7 \pm 2.31$  Torr and  $1.4 \pm 0.2$  Torr (cf. Table 1), while administration of rHSA-Heme shows increase in the oxygen partial pressure in the tumor tissues up to 3.5 Torr after a lapse of 400 seconds (cf. Fig. 1, data for the rHSA-Heme treated group). This demonstrates the fact that the porphyrin metal complex-clathrate albumin compound of the present invention can pass easily through the irregular blood vessels in the tumor tissues because of its small molecular size as compared with the red blood cells.

In contrast therewith, the primary partial pressures of oxygen (P02) at the normal sites and tumor sites of the right leg of the rHSA treated group were  $14.8 \pm 2.8$  Torr and  $1.7 \pm 0.2$  Torr (cf. Table 1, rHSA treated group), and the sole administration of rHSA shows no increase in oxygen partial pressure (cf. Fig. 1, data for the rHSA treated group).

The above results demonstrate the facts that no oxygen transport is taken place without presence of Heme and that the porphyrin metal complexclathrate albumin compound of the present invention can effectively increase the oxygen partial pressure in the tumor tissues. This demonstrates a truly unexpected result over the conventional art.

*Distinctions Of The Invention Over Tsuchida I and Tsuchida II*

Tsuchida I discloses that tetrakis-(o-(pivalamido) phenylporphyrinatoiron(II) derivatives (FePs) are incorporated into hydrophobic cavities of recombinant human serum albumin (rHSA), providing a synthetic O<sub>2</sub>-carrying hemoprotein (rHSA-FeP) and teaches that the O<sub>2</sub>-binding affinity and O<sub>2</sub>-association and dissociation rate constants of resultant rHSA-FeP satisfy the initial clinical requirements for O<sub>2</sub> infusion as a red cell substitute (see Abstract of Tsuchida I).

However, Tsuchida I fails to teach or suggest the effects of the porphyrin metal complex-clathrate albumin compound on the oxygen partial pressure in the tumor tissues. That is, Tsuchida I fails to teach or suggest an “oxygen infusion for increasing an oxygen concentration in tumor tissues in living bodies,” such as is set forth in claim 1 of the present invention. Therefore, Tsuchida I fails to be usable as the basis of an assertion of obviousness.

On the other hand, Tsuchida II discusses that human serum albumin (HSA) incorporating synthetic hemes, the tetrakis-(o-pivalamido) phenylporphyrinatoiron (II) derivative (FeP), is an artificial hemoprotein (HSA-FeP) which is able to reversibly bind and release dioxygen under physical conditions like hemoglobin and myoglobin (see abstract of Tsuchida II). Based on the evaluation of physiological responses to exchange transfusion with HSA-FeP solution into rats after hemodilution and hemorrhage, Tsuchida II that the declined mean arterial pressure (MAP) and blood flow after 70% exchange with HSA and the further 40% bleeding of blood was recovered up to 90% of the baseline values by injection of HSA-FeP. However, Tsuchida II fails

to teach or suggest the effects of the porphyrin metal complex-clathrate albumin compound on the oxygen partial pressure in the tumor tissues. Tsuchida II thus fails to address the deficiencies of Tsuchida I in teaching or suggesting a claimed embodiment of the present invention.

In contrast, the paragraph bridging pages 4-5 of the specification discusses that cancer cells are in a hypoxic condition, and the presence of the hypoxic cells is one of the reasons that malignant tumors have resistance to radiotherapy or chemotherapy. Thus, the behaviors of porphyrin metal complex in normal cells differ from that of porphyrin metal complex in cancer cells.

Although attempts to improve anticancer properties and radio sensitivity by increasing the oxygen concentration of the tumor tissue in low-oxygen conditions have been made, there remains a significant problem to be solved, as is discussed in the paragraph bridging pages 6-7 of the specification.

According to the present invention, this problem is solved by use of a porphyrin metal complex-albumin clathrate compound which has a particle size smaller than that of red cells and is able to find a path through irregular blood vessels in the tumor tissue easily, as compared with red blood cells, which in turn makes it possible to effectively increase the oxygen partial pressure in the tumor tissues. Such an effect of the present invention is never expected from the cited references, and thus the present invention is never obvious from the cited references, considered alone or in combination.

As a result, the combination of Tsuchida I and Tsuchida II would fail to motivate one of ordinary skill in the art to produce claim 1 of the present invention. A *prima facie* case of obviousness has thus not been made.

Moreover, Applicants submit that the Examiner is engaging in impermissible hindsight reasoning in order to arrive at the presently claimed invention. As stated in MPEP § 2142, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.

The Examiner states in the rejection that one of ordinary skill would modify the compound of Tsuchida II as taught by the compound of Tsuchida I because such a change is considered “routine structural optimization and because “it binds oxygen better.” However, a particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of an optimum variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). (Emphasis added) The Examiner has not provided any basis for the conclusory statement that the modification of Tsuchida II by Tsuchida I is advantageous because it allegedly binds oxygen better. Thus, Applicants submit that the outstanding rejection is improper and request withdrawal of the rejection.

Claims depending upon claim 1 are patentable for at least the above reasons. Also, the present invention shows unexpected results over the cited references, as has been discussed above.

This rejection is overcome and withdrawal thereof is respectfully requested.

### **Conclusion**

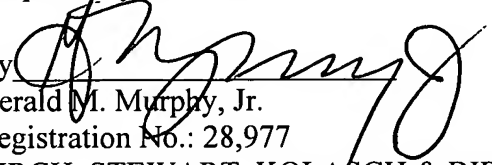
In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Gerald M. Murphy, Jr., Reg. No. 28,977 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

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